DISSERTATION

MORBIDITY PATTERN AND OUTCOME OF THERAPY IN UNDERNOURISHED CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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CERTIFICATE

This is to certify that the dissertation titled **"MORBIDITY PATTERN AND OUTCOME OF THERAPY IN UNDERNOURISHED CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA"** submitted by Dr.V.PRATHIBA to the Faculty of pediatrics, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree(Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance

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INTRODUCTION

Leukemia has been the focus of immense research and progress over the last century. The most common subtype, acute lymphoblastic leukemias (ALL) accounts for 75% - 80% of all childhood leukemias, with acute myeloid leukemia comprising 20% and chronic myeloid leukemia around 2%. Survival rates for ALL have improved dramatically with a current five-year overall survival rate estimated at 78 to 85 percent.1,2,3,4 Improvement in survival is due to treatment of a large number of children on sequential standardized research protocols. Eighty - ninety percent of children with newly diagnosed ALL participate in such trials, the goals of which are to improve clinical outcomes while minimizing acute toxicities and late-occurring adverse events. Event-free survival (EFS) rates for ALL have also steadily improved since the 1980s. The overall five-year EFS for childhood ALL currently approaches 80 percent in the developed world, and the ten-year EFS is about 60 percent 5. The five and estimated ten-year survival rates for patients diagnosed from 2000 to 2004 were 88 and 84 percent, respectively 6. The ten-year survival rate for children diagnosed in the 2005 to 2009 period is estimated to be 88 percent.

In contrast, in the developing world, cure rates are less than 35 percent 7.The main reasons include late presentation , difficulty in accessing health services , poverty , non compliance to therapy and lack of dedicated paediatric oncology units.

The population of India recently exceeded a billion people. Almost 50% are less than 25 years of age. Although complete data for India are not available, population-based data from various Indian cancer registries suggest that approximately 10,000 new cases of acute lymphoblastic leukaemia (ALL) occur each year in the <25 year age group. A small percentage of these patients are adequately treated, and the majority die from the disease. This contrasts with present cure rates of over 80% in Western countries. India faces problems as in

all other developing countries which includes paucity of cancer treatment facilities, lack of human and physical resources required for effective management (both of which lead to lack of access to effective medical care), poverty and low level of education of the population. Also included are delay in diagnosis and consequent presentation with more advanced disease and high rate of abandonment of therapy with subsequent loss to follow-up.

Malnutrition is an adverse prognostic factor in the outcome of treatment in patients with acute lymphoblastic leukemia. Undernourished children do poorly as compared with well nourished children. The reasons cited are many and include malnourishment leading to a

diminished bone marrow reserve resulting in delivery of suboptimal doses of maintenance chemotherapy (less than that calculated according to body surface area).

Depletion of nutritional reserves and significant weight loss can lead to an increased risk of morbidity, reduced chemotherapy response, and shorter survival in patients with cancer. Weight loss and malnutrition are recognized to result from multifactorial processes, which if assessed and managed appropriately may lead to improved treatment outcome.

The prevalence of malnutrition in India is 45.9% as per National Family Health Survey of India 3(2005 – 2006). We would expect the same prevalence, if not

higher, in children presenting with leukemia. With this in mind, the plan for our study is to compare the outcome of well nourished versus undernourished children who are treated for ALL in the hematology unit at the Institute of Child Health.

REVIEW OF LITERATURE

The leukemias are the most common malignant neoplasms in childhood, accounting for about 40% of all malignancies that occur in children less than 15 years of age . Acute lymphoblastic leukemia accounts for about 75 % of cases of childhood leukemia, acute myelogenous leukemia for about 20%, chronic myelogenous leukemia 2 -3 % and juvenile chronic myelogenous leukemia about 1 – 2%..

Childhood ALL was the first disseminated cancer shown to be curable and consequently has represented the model malignancy for the principles of cancer diagnosis, prognosis and treatment. It is actually considered as a heterogenous group of malignancies with a number of distinctive genetic abnormalities that result in varying clinical behaviours and responses to therapy. Appropriate risk assessment has over the years been found to be the most important factor in the selection of therapy. The outcome of ALL is dependent on a number of factors. The most crucial factors include the clinical features, cytogenetics of the leukemic cells, pharmacodynamics, pharmacogenetics and early treatment response. It is the research on the interplay of these factors and the use of risk adapted treatment protocols which has resulted in nearly 80% survival at the turn of the millennium.

Outcome of Acute lymphoblastic leukemia

In Developed countries

The prognosis of childhood acute lymphoblastic leukemia (ALL) has improved greatly in the past 40 years. Current literature report on a long-term event free survival (EFS) of about 75% and overall survival(OS) of about 80% in developed countries.

In the Nordic countries the 5 year event free survival of childhood ALL has increased from 57% to 77% in the past 2 decades and the current figures give an EFS of 79%.[10]

In another study done in Spain between 1989 and 2005 , 50 patients were analysed and the 5 yr EFS was 78% with the OS being 87.8%.[11]

Recent figures from United Kingdom using the UKALL 97/99 protocol give an event free survival of 78%, an improvement of nearly 8 -10% from a decade earlier.

In a study done in Kyushu University, Fukoaka Japan on 62 patients with ALL, the 10 yr EFS was 80.6±5 % and the OS was 88.7± 4% after a median follow-up time of 9.3 years.[12]

In the United States, there are approximately 2,400 children and adolescents younger than 20 years of age diagnosed with ALL each year .Seventy-five percent to 80% of children with ALL survive at least 5 years from diagnosis with current treatments that incorporate systemic therapy (e.g., combination chemotherapy) and specific central nervous system (CNS) preventive therapy (i.e., intrathecal chemotherapy with or without cranial irradiation).[13,14,15,16]

In developing countries*:*

More than 80% of the world's children live in less-advantaged countries, where the cure rate generally does not exceed 35%. Patients with ALL in developing countries often present with more advanced disease. Co-morbidities such as hepatitis, malaria and malnourishment are also more common, which may affect the patients' ability to tolerate treatment. Access to care in cancer centers or pediatric oncology units is much more limited in developing countries, and patients and their families often have to travel long distances to reach major hospitals for the diagnosis and/or providing necessary treatment. Further, even when they reach these centers, a family's inability to pay for treatment due to socioeconomic factors or the lack of health insurance has a major impact upon the type of therapy that is ultimately provided to the child. Continuation of treatment and follow-up is often difficult, again because of socioeconomic factors, the need to travel long distances, and the lack of trained physicians who can manage their care outside the major cancer center or pediatric oncology unit. This results in a high default rate.

In a study in China from 1998 to 2007 on 329 (203 males and 126 females) newly-diagnosed cases of childhood ALL, the overall EFS at 5 years was (68.0 ± 5.0) %.All the children were treated with ALL XH 99 protocol. Patients were classified into low risk (LR), medium risk(MR) and high risk (HR) on the basis of their presenting clinical features, biological features and early response to remission induction treatment. The EFS rates at 5 years in LR, MR and HR groups were (83.0 ± 6.0) %, (78.0 ± 14.0)

% and (39.0 ± 10.0) %, respectively (P <0.05).[19]

In a study in El Salvador done between 1994 and 1996 , 153 children with ALL were included. They were treated with the modified SJCRH protocol. High risk was defined as: DNA index < 1.16, age 12 months or younger, white blood cell count > or = 50 x 10(9)/L, T-cell immunophenotype, anterior mediastinal mass, central nervous system leukemia at diagnosis, or t(4;11), t(1;19), or t(9;22).The overall 4 yr survival rates were 48± 6%. The 4-year EFS rates in patients at high-risk and standard-risk were 46 ±7% (n = 121) and 69 ±15% (n = 16), respectively (P = 0.20).[21]

A study was conducted in China on 58 children with ALL between 1998 and 2003. The 5 yr EFS in this study was 51.3%.It was also concluded that when compared with industrialized countries, children with ALL have a lower remission rate, a lower 5-year EFS, and a higher mortality from sepsis.[22].

In 2009, a Chinese study on 91 children with ALL has given an EFS of 52.3 % at 4 years. The treatment related mortality has been seen to be 3.3% and treatment abandonment as 24.2%.Treatment abandonment is a major cause of treatment failure in China.[23].

The causes of treatment failure in childhood acute lymphoblastic leukaemia are thought to differ between resource-rich and resource-poor countries. In a study in Honduras,168 children with ALL were analysed. Abandonment of therapy was the main cause of treatment failure. Treatment failure was also associated with prolonged travel

time to treatment facility and age less than 4.5 years.[24]

The National Chilean Pediatric Oncology Group, PINDA conducted a prospective nonrandomized trial using a modified version of the Berlin-Frankfurt-Munster protocol (ALL BFM 86) from June 1987, to June 1992,on 425 patients with ALL. Therapy was stratified by risk as standard, high and very high risk. The overall 5-year event-free survival (EFS) rate was 60% ± 2% (SE). The 5-year EFS rate for each risk group

was: SR 75%, HR 62%, VHR 28%, with a median follow-up of 6.5 years (range 4.5-9.5 years).[25]

Outcome of ALL in India:

In the 1970s, survival rates after treatment for acute lymphoblastic leukaemia (ALL) in children and young adults (less than 25 years) in India were poor, even in specialised cancer centres.

The earliest ALL studies in India during the 1970s were conducted at the Tata Memorial Hospital in Munbai and the 3 year survival has seen to be 22%. In the 1980's with more aggressive therapy and improvement in supportive care the EFS at 5years had improved to 32%.

There have been a few studies on the outcome of ALL in India. A multicentric trial done by the International Network for Cancer Treatment and Research where 3 Indian hospitals: Cancer Institute , Chennai ; Tata Memorial Hospital ,Mumbai and All India Institute of Medical sciences, New Delhi contributed data, a 5 year survival rate

between 45% and 60% was seen. This includes higher rate of toxic deaths and extensive disease partly attributable to delayed diagnosis. It has been felt that the risk factors defined in the western population cannot be assumed to be equally appropriate for risk adapted therapy in less affluent

countries. The heterogenicity in patient population can result in significant differences in outcome.[8]

Differences in the patient populations between the developed world and India has been noted. In a multicentric trial in India, total white blood cell count (WBC) was the only statistically significant risk factor identified in multivariate analyses. Age is strongly associated with outcome in Western series, but was not a risk factor for EFS in any of the Indian centres. Comparison of patient characteristics with published series from Western nations indicated that patients from all the Indian centres had more extensive disease at presentation, as measured by WBC, lymphadenopathy and organomegaly. The worse outcome of treatment in Indian patients compared with recent Western series was probably due to the higher rate of toxic deaths in the Indian patients, and possibly also due to their more extensive disease – which is, at least partly, a consequence of delay in diagnosis. Differences in the spectrum of molecular subtypes may also have played a role. The higher toxic death rates observed are likely to have arisen from a combination of more extensive disease at diagnosis, co-morbidities (e.g., intercurrent infections), differences in the level of hygiene achievable in the average home, poor access to acute care, and more limited supportive care facilities in Indian

hospitals. Since the prevalence of individual risk factors varies in different populations . and over time, their relative importance would also be expected to vary in different centres and in different time periods. These findings have important implications for the treatment of ALL in countries of low socioeconomic status. It cannot be assumed that risk factors defined in Western populations are equally appropriate for patient assignment to risk-adapted therapy groups in less affluent countries.

A study was done in All India Institute of Medical Sciences from June 1992 to June 2002 where 250 children up to 15 years age with newly diagnosed ALL were included and were uniformly treated on MCP 841 protocol. There was a male preponderance (male: female-3.8: 1).The event free and disease free survival rates were 67.5 % and 51.6% respectively.[26]

In another study done in Institute for Child Health and Hospital, Chennai during the period of June 1991 to December 1995, the outcome of 135 children with ALL was analysed . Seventy children (53 per cent) were treated with a high risk protocol, 25 (17 per cent) received an intermediate risk, and 40 patients (30 per cent) received a standard risk protocol. Analyzing the outcome in 135 children, 34 (27 per cent) had event free survival (EFS) at the time of analysis; of these 41 per cent had EFS after 2 years of therapy, 31 per cent after 3 years and 18.7 per cent after 4 years (i.e. 1 year after stopping 3 years of therapy). Fifty-seven

children (41 per cent) dropped out; 25 (18 per cent) died due to sepsis. Treatment obstacles included delay in diagnosis, poor health education and facilities, poor

supportive care, and socio-economic problems.[27]

In a retrospective analysis in a Government Medical College in Kerala 79 patients with acute lymphatic leukemia treated from January 1990 to June 2006 were analysed. Of the 73 patients who completed treatment, 23 survived (36%); 20 had event-free survival more than 5 years after remission.[28]

In a study done in Vellore, three hundred and seven children (1-14 years) with acute lymphoblastic leukemia (ALL) were treated with a modified BFM protocol 76/79 between 1985 and 2003. Treatment outcome and prognostic factors were evaluated. The median event free survival (EFS) was 114 months. The estimated 5 year overall survival, EFS and disease free survival was 59.8%, 56%, and 53.9%, respectively.[29]

In a study done in Cancer Institute, Chennai from 1990 to 2001,345 children with ALL were diagnosed and their survival rates were calculated. The absolute survival rates at 1 , 3 , 5 and 10 years were 58.6%,40.5%,36.3% and 29.8% respectively.[8]

The factors predicting the outcome to treatment of children with ALL include: age ; sex ; race ; liver and/or spleen enlargement ; morphology (French-American British Cooperative Group (FAB)) of the blast-cells ; immunologic phenotype of the blast-cells , white blood cell count (BC) at diagnosis ; platelet count at diagnosis ; central nervous system CNS) leukaemic infiltration at diagnosis ; glucocorticoid receptors in the blast-cells ; Periodic acid shift (PAS) reactivity of the blast cells; time to

achieve complete remission ; chromosomal abnormalities , number of blast cells in DNA synthesis phase .[9]Malnutrition has also been quoted as adverse prognostic factor in ALL especially in the developing countries

Nutrition and cancer :

Malnutrition is found in 10 -50-% of children with cancer in industrialized countries. In developing countries a large proportion of the normal pediatric population is undernourished and children frequently present late with advanced disease.

Cancer-associated malnutrition can result from local effects of a tumour, the host response to the tumour and anticancer therapies. Cancer patients often have reduced food intake due to systemic effects of the disease, local tumour effects, psychological effects or adverse effects of treatment. In addition alterations in nutrient metabolism and resting

energy expenditure (REE) may also contribute to nutritional status. Several agents produced by the tumour directly, or systemically in response to the tumour, such as pro-inflammatory cytokines and hormones, have been implicated in the pathogenesis of malnutrition and cachexia. The consequences of malnutrition include impairment of immune functions, performance status, muscle function, and quality of life. Also, responses to chemotherapy are decreased, chemotherapy-induced toxicity and complications are more frequent and severe, and survival times are shortened. Depression, fatigue and malaise also significantly impact on patient well-being. In addition, cancer-related malnutrition is associated with significant healthcare-related

costs. Nutritional support, addressing the specific needs of this patient group, is required to help improve prognosis, and reduce the consequences of cancer-associated nutritional decline.[31]

There exists a relationship between malnutrition and poor prognosis of patients with acute lymphoblastic leukaemia . It has been shown that undernourishment is an adverse prognostic factor in the outcome of treatment of patients with ALL in malnourished children. Due to diminished bone marrow reserve, these children receive approximately 50% of the optimal doses of so-called "maintenance" chemotherapy, thus leading to frequent bone marrow leukaemic relapses and hence a shortened disease-free survival.[32]

In a study done in Spain in 43 patient ,many variables including age, sex ,WBC at diagnosis, FAB morphology, CALLA/CD 10 reactivity of the blast cells, lymph node, liver or spleen enlargement, site of treatment and malnutrition were analyzed in the outcome of treatment. Of these variables only malnutrition had a significant impact on survival. Undernourished children($n = 16$) had a significantly worser outcome than well nourished children($n=27$). The 5 year survival rate was 83% for well nourished children and only 26% for undernourished children($p < 0.001$). Bone marrow relapses presented more in the undernourished than the well nourished. The doses of maintenance chemotherapy had to be reduced in 68% of undernourished and 10% of well nourished children. It has been seen that those with a mild to moderate degree of undernourishment do better than those with severe forms of malnutrition (2

year-DFS was 50% and 25% respectively, p less than 0.02), but significantly worse than those with normal nourishment status (5 year DFS 83%).[9]

In another Mexican case control study, the effect of severe malnutrition on the mortality of 17 children with ALL during the initial induction-to-remission phase of the treatment was studied. These 17 cases

were compared with 76 controls who had survived the phases of induction and consolidation. It was found that the chance of dying during the initial phase of the treatment was 2.6 times higher in undernourished children with ALL than in those children with normal nourishment status. The risk of death increased with the severity of undernourishment ($p = 0.04$).[33]

In a study in Guatemala, some degree of nutritional depletion was seen in up to 54% of newly diagnosed children with acute lymphoblastic leukemia. Nutritional status was determined by arm anthropometry (mid upper arm circumference and triceps skin fold thickness) .Deaths due to abandonment of therapy and treatment failure were more common in under-nourished than in well-nourished children.[34]

Undernourishment is an adverse prognostic factor in the outcome of treatment of patients with ALL. Malnourished children, due to their diminished bone marrow reserve, receive approximately 50% of the optimal doses of so-called "maintenance" chemotherapy, thus leading to frequent bone marrow leukaemic relapses and a shortened disease-free survival.

The delivery of sub-optimal doses of myelosuppressive maintenance

chemotherapy is by itself, an adverse prognostic factor in the outcome of treatment of children with ALL.

In another Mexican study it has been seen that five year disease free-survival was 65% and 7% for children receiving either optimal and sub-optimal doses of maintenance chemotherapy (p less than 0.001) respectively . Accordingly, suboptimal doses of chemotherapy were delivered mainly in undernourished children, due to the abnormally low bone marrow reserve . The degree of undernourishment is related to the prognosis and also the changes in the nutritional status along with the anti-leukemic chemotherapy, have an impact on the prognosis.[35]

The nutritional status of a cohort of children treated for acute lymphoblastic leukemia was studied in Cuba. The study involved 49 children admitted to a single center and treated with a Berlin-Frankfurt-Munster-based protocol. Nutritional assessment included measurements of height, weight, body mass index and skin-fold thickness, at diagnosis, after the intensive phase of treatment and at the end of therapy. There were no statistically significant differences between the results at diagnosis, after intensive therapy and at the end of treatment[36]

Malnutrition has a negative impact on treatment outcome of hospitalized patients and results in increased morbidity and mortality in ALL patients. Malnourished patients have up to 20 times more complications than well- nourished patients.[8]. The effects of malnutrition

on patient outcomes are dramatically demonstrated in morbidity and mortality studies.

In a study done in Mexico on 500 patients with ALL in which 376(75%) were well nourished and 124(25%) were malnourished, the 5 year survival for well nourished was 59% compared to 26% in undernourished children .The relative risk of dying was 1.8 times higher for undernourished than the malnourished. The correlation between malnutrition and compromised treatment was 0.92. Malnutrition might be included as an adverse prognostic factor in acute lymphoblastic leukemia .[37]

A few studies have shown no relationship between malnutrition and the outcome of ALL. A study was performed in a cancer centre in Lahore. One hundred patients with ALL below the age of 14 years were included in this study.They were treated as per guidelines of the BFM protocol. Patients were classified according to Waterlow classifications of malnutrition (1976). Group-I, as Undernourished children (UNC) and Group-II as wellnourished children (WNC). Percentages in both groups were found out with respect to total expired, relapses and completed treatment.In Group-I (UNC) 44.5% completed treatment and are alive, 9.5% relapsed and 46% expired. In Group-II (WNC) 59.5% completed treatment and are alive, 5.5% relapsed and 35% expired. There was no

statistical difference in the survival between the WNC and the UNC($p=0.791$).[38]

A study was done at the National Institute of Paediatrics, Mexico on 100 patients with ALL.. The study aim was to correlate malnutrition and early death in children with acute lymphoblastic leukemia. An analysis included clinical and

laboratory parameters as well as co-morbidity factors. Forty patients were standard risk and 60 were high risk. Malnutrition.(p =1) and poverty(p = 0.5) had no role in the outcome of the disease.[39]

According to a study in United Kingdom done on 78 children with ALL, Reilly et al, reported that weight for height does have an influence on outcome in ALL, but the mechanism is unclear and the finding requires confirmation by large scale prospective studies.[(41)]

Chemotherapy and bone marrow reserve:

Haematopoietic toxicity is often a side effect of cytotoxic chemotherapy. The degree of aplasia and rapidity of count recovery following chemotherapy are indicative of bone marrow reserve. Patients who have a normal bone marrow function will recover from chemotherapy induced cytopenia relatively rapidly. In contrast patients with poor bone marrow reserve will possibly have prolonged period of aplasia.[42]

The degree and duration of toxicity varies according to the agent used, dose and rate of administration. [43].Bone marrow cells are particularly sensitive to damage inflicted by alkylating agents. Antimetabolites cause a decrease in granulocyte counts within 7 days that lasts no longer than 21 days. The effect of cytotoxic agents on bone marrow may be felt after many years .

Factors Affecting Bone Marrow Reserve

The ability of bone marrow to withstand cytotoxicity is directly related to bone marrow reserve and to the presence of functional stem cells [44,45.] The degree of myelosupression

depends not only on the particular agent used but also on its dosing, amount of exposure and scheduling. The exact mechanism by which different chemo-therapeutic agent achieve myelotoxicity is not fully understood.*In vitro and vivo* data indicate that decrease in bone marrow reserve is associated with a decrease in stem cells repopulating ability. Severe decrease in peripheral blood count, marrow cellularity, stem cell content, self-renewal capacity and long term survival was seen in mice treated with drugs that are toxic for stem cells. Different patient populations respond differently to the same chemotherapy.

Malnutrition and Bone marrow reserve

Protein-calorie malnutrition (PCM) also known as protein-energy malnutrition is defined by the World Health Organisation (WHO) as being " a group of pathological conditions that is a result of a lower ingestion, in various proportions, of protein and calories. This occur more frequently in children less than five years of age and is commonly associated with infection.[46]

Malnutrition may originate from the deficiency or absence of any nutrient. The establishment and severity of a state of malnutrition depends on the cause, intensity and duration of nutritional deficiency. It can be caused by (i) an inadequate diet (ii) by deficiency in gastrointestinal absorption (iii) deficient ingestion or increase in demand, (iv) an excessive excretion of nutrients.

Protein-calorie malnutrition (PCM) is usually found in children, the elderly, patients

suffering from neoplasia or chronic disease, patients undergoing chemotherapy, or even patients under parenteral nutrition. PCM presents a wide spectrum of signs and symptoms that are a result of not only the cause(s) that led to malnutrition, but also of the different degrees of protein or carbohydrate deficiency. The implications of modifications of the haemopoietic environment in malnutrition states are still obscure, however, they seem to be responsible for inefficient

haemopoiesis, especially inefficient myelopoiesis, and they seem to be irreversible over the short term

Factors affecting haemopoiesis –The Physiology

Blood, as a tissue is characterised by *(i)* its high rate of renewal, taking into account that its mature cells present a relatively short lifetime in circulation;[47] and *(ii)* its flexibility and ability to adapt to different physiopathological conditions.

Physiologically, in human adults, haemopoiesis occurs in the bone marrow. The constant production of cells depends on the microenvironment of the marrow, an organised structure that regulates the physiology of the haemopoietic stem cells.[48,49,50]

The microenvironment is constituted by haemopoietic cells in different states of maturation, stromal cells (reticular cells, macrophages, endothelial cells, adipocytes), by an extracellular matrix (ECM) and by soluble substances, [51,52,53] in what is a compartmentalised, dynamic structure, that in addition to supplying parenchymal support for the haemopoietic cells, provides a "biochemical environment" that is

fundamental for their proliferation, differentiation and maturation.

Regulatory factors that make up inductive microenvironments are considered to exist.[54,55,56]

Haemopoiesis is influenced by several stimuli that act at different levels in the process. For this reason, cell-cell and cell-stroma interactions that occur in both the haemopoietic inductive microenvironment and other locations must be considered.[57] As should the action of the different growth factors and cytokines, hormonal action - especially that of the estrogens, androgens, thyroid hormones, corticosteroids and epinephrine, plasmatic and cellular mediators of the inflammatory response and, obviously, the nutritional state of the individual.[58,59,60]

Malnutrition and Erythropoiesis*:* Anaemia

The haemopoietic tissue, like all tissues that present a high rate of renewal and cellular proliferation, has a high demand for nutrients. The sheer need for protein by the process of haemopoiesis could in itself justify the occurrence of anaemia and leucopenia which are frequently encountered in malnourished individuals.

PCM is a syndrome in which anemia together with multivitamin and mineral deficiency may be present. According to Vilter

(1975), children with typical PCM present normochromic, normocytic anaemia, with haemoglobin levels that lie between 8 and 10 g/dL and normal medullary erythropoiesis, or a discretely hypoplastic marrow with fatty infiltration.[61]

Malnutrition and Leucopoiesis*:*

Protein malnutrition induces structural alterations in lymphoid organs, especially in thymus-dependant areas.[62,63,64,65] Protein deficiency leads to lymphopenia, thymus, spleen and lymph node involution, which is particularly intense in the thymus and spleen.[66,67,68,69,70] Aschkenasy (1966b) reported atrophy of the thymus and lymph organs, with a pronounced reduction in cellularity, especially in thymus-dependant areas.

The different lymphocyte populations seem to be affected by malnutrition differently: in thymus-dependant areas, there is a reduction in the number of T-lymphocytes, especially the $CD4^+$ population, whereas the number of B-lymphocytes in the spleen, lymph nodes and blood remain normal.

Existing data on humoral response are conflicting, which makes definitive conclusions hard to reach.[62] The concentrations of IgA,
IgG and IgM can be, increased,[71], or normal or decreased.[72] IgE is found at a higher concentration in malnourished children.[73]

It has been shown that though immunoglobulin concentrations may seem to be normal in malnutrition, functional studies involving B-lymphocytes indicate that the type and intensity of a response to various antigens is altered.

Febrile neutropenia*:*

Fever is the principle sign of infection in neutropenic patient and frequently may be the only evidence of infection. The pattern of fever in neutropenia is non-

specific and not pathognomonic of any type of infections or non-infectious process and can be suppressed by the antipyretic effects of drugs such as corticosteroids. Neutropenia, resulting from cytotoxic chemotherapy is the most common risk factor for severe infections in hematological malignancies. The duration of neutropenia also contributes significantly to the risk of serious infections. This risk is significantly greater with a lower neutrophil counts, such that 100% patients with ANC <100 cells/microl lasting 3 weeks or more develop documented infections. The prompt initiation of empirical antibiotics in febrile neutropenia has been the most important advance in the management of the immunocompromised host.

Fever is associated with malignancy and is a common problem in cancer patients When fever appears, a series of diagnostic and therapeutic measures must be taken even if precise knowledge of the cause of the infection is lacking. Fever can be caused by infection or by the cancer itself through tumor-related necrosis, hemorrhage or pyrogens. Infection is the commonest cause, however. Bacterial and fungal sepsis can coexist and the bacteremia can overshadow the more difficult to determine fungal infections.

Definition of febrile and neutropenia

The consensus guidelines from the immunocompromised host society state that a single oral temperature of 38.5 C or more, or the occurrence of three

temperatures of 38 C or more within a 24hours period, taken at least 4hours apart, is defined as fever in a neutropenic patient. Neutropenia is defined as an absolute neutrophil count (polymorphonuclear cells plus band forms) of 500/ml or less. From a practical stand point patients with ANC between 500 and 1000 cells/ml and rapidly falling ANC because of chemotherapy are considered to be at risk for febrile neutropenia.[74]

The criteria of febrile neutropenia should be defined and rigidly adhered to as a signal for the initiation of empirical antibiotic therapy , which plays an important role in reducing infection related morbidity and mortality in neutropenic patient with fever.

Impaired host defences in haematological malignancies :

Patients with hematological malignancies are immunocompromised as a result of the underlying malignancy or due to the therapeutic interventions employed to manage it. Some malignancies are associated with specific immune defects that predispose to infections with particular pathogens . Patients with acute leukemia have increased risk of severe gram-negative bacterial infections as a result of quantitative or functional neutropenia. Patients with chronic lymphocytic leukemia and multiple myeloma are susceptible to invasive bacterial infections from staphylococci and streptococci especially pneumococcus. Conversely patients with lymphoma have abnormalities of the cellular immune system resulting in an increased risk of viral infections (e.g. herpes simplex) and fungal infections (e.g. Cryptococcus).

The duration of neutropenia also contributes significantly to the risk of serious infections. This risk is significantly greater at lower neutrophil counts, such that 100% patients with ANC <100 cells/ml lasting 3 weeks or more develop documented infections. Qualitative

defects in neutrophil function have been described in hematological malignancies. These include defects in chemotaxis, phagocytosis, bactericidal capacity, and absence of respiratory burst that accompanies phagocytosis.

Febrile neutropenia and malnutrition:

The incidence of febrile neutropenias is clearly more in malnourished children than in normally nourished children. This is mainly due to diminished bone marrow reserve seen in undernourished children.

In a study done in Maulana Azad Medical college,New Delhi, the nutritional status of 44 children with newly diagnosed ALL was evaluated by anthropometric, hematological and biochemical parameters before initiating therapy and response to therapy was assessed during follow up. Malnutrition was seen in 56.8% children by weight for age criteria. Complications like febrile neutropenia and bleeding were more in the malnourished group.the incidence of febrile neutropenia was 28% in the well nourished group when compared to 32% in the malnourished group. A statistically significant higher incidence of infection was seen in the malnourished group[75]

In another study done in Tata Memorial hospital ,Mumbai on 530 patients with ALL from 1986 to 1993, it was shown that nutritional status could be relevant to toxic death, and there was some evidence that height for age and weight for age had a greater impact on toxic death than on disease progression. Patients with height for age and weight for age patients below the median for each had a greater risk of dying from toxicity *(P* = 0.049 for height for age and *P* = 0.023 for weight for age). Such patients also had an approximately 2.6-fold greater risk of dying from toxicity than from progressive disease.[76]

Chemotherapy dose modifications—delays of the next cycle and/or dose reductions—are another common consequence of neutropenia and are implemented due to a slow recovery of the bone marrow after a previous course of chemotherapy. Recent practice pattern studies have shown the extent to which community oncologists delay and reduce the doses of the chemotherapy. In addition to the direct effects of neutropenia on the risk of infection and quality of life, there is evidence that neutropenia is associated with exacerbations of other adverse effects of chemotherapy. Whether the occurrence of neutropenia predicts the occurrence of other adverse events or whether neutropenia itself has a causal role in these events is not clear.

JUSTIFICATION OF THE STUDY

Acute lymphoblastic leukemia is the most common malignancy in childhood

.it accounts to ¼ th of all childhood malignancy .Children with ALL have an overall chance of survival of 80% in western countries and 60% in developing countries. Despite significant advances in supportive care during last few years, infection remains the major cause of morbidity and death. These results from combination of factors 1)limited supportive care resources in hospital 2)extensive disease at diagnosis 3)poor socioeconomic factors 4)malnutrition. Malnutrition has been cited as an important cause of morbidity in these children. Undernourished children do poorly as compared with well nourished children because of reduced bone marrow reserve ,thus making necessary delivery of suboptimal doses of chemotherapy.

This proposed study is designed to determine the morbidity and outcome of therapy in undernourished children with ALL.

AIM & OBJECTIVES

To determine the morbidity and mortality pattern amongst children who have received the treatment for ALL & impact of nutritional status on the morbidity &outcome of the therapy

STUDY DESIGN:

Retrospective cohort study(serial data analysis)

Consent form:

Institutional consent was obtained to retrieve data

MATERIALS AND METHODS:

This study was carried out in the hematology unit of Institute of child health. Data was retrieved from the case records of Pediatric case sheets. Children who were started on treatment from January 1st 2000 to December 30th 2006 were the subjects in the study.

All these children were treated on the BFM protocol

201 children with ALL were studied

Inclusion criteria:

All children who opted for treatment for ALL during the year January 2000 –December 2006

Exclusion criteria:

Patients who presented with relapsed disease.

Children treated on a different protocol

No of patients: 201 patients were studied

METHODOLOGY :

Data and diagnosis of patients registered in the Pediatric hematology clinic was maintained . The file number of children with ALL between the period January 2000 and December 2006 were recorded and the files were retrieved from the medical

records department of Institute of health child. The relevant information were extracted, and recorded on a predesigned profoma. Particular emphasis was laid on extracting the following information

- Demographic profile, symptomatology, clinical features, height, weight, investigations, treatment, follow up and outcome. The nutritional status was determined by the WHO standards ¨The data was analysed subsequently. Data concerning morbidity during treatment was recorded[27]. This includes

Need for blood transfusion

Need for platelet transfusion

No of children had febrile neutropenia

Any infection during the treatment

Relapse

Mortality

The date of last evaluation of the child was the end point

Nutritional status:

The nutritional status of the child was assessed by weight for age and based on the WHO standards the study group was classified as well nourished & undernourished

Weight less than 2 standard deviation(<-2 z) were classified as undernourished

Weight more than 2 standard deviation as normal nourished

Febrile neutropenia:

Febrile neutropenia refers to the clinical presentation of fever(one temperature ≥ 38.5 C or three readings ≥ 38 C but less than ≤38.5 C per 24 h) in a neutropenic patient with an uncontrolled neoplasm involving

the bone marrow or more usually in a patient undergoing treatment with cytotoxic agents.[79]

Infections :

The number of children who had infection was documented which includes pneumonia ,hepatitis ,HbsAg positive patients ,meningitis, urinary tract infections & sepsis

Statistical analysis:

The mean and standard deviation of all quantitative parameters was calculated

Percent occurrence rate (Frequency) in respect of different morbidities experienced by the sample subjects was calculated.

Chi square test was applied to quantify extent of intergroup (well nourished versus undernourished) differences.

By logistic regression analysis ,independent predictors of outcome was calculated

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RESULTS:

Total no of children enrolled in this study was 201.

Age distribution :

Mean age at presentation was 5.8 years range (4 months -12 years)

AGE (Years)	NO OF CHILDREN	PERCENTAGE
<1	11	5.5%
1-5	94	46.8%
>5	96	47.8%
	201	100%

Sex distribution:

MALE	FEMALE
140	61
69.7%	30.3%

In the present study, 69.7% were males and 30.3% were female .the difference was statistically significant with p valve 0.003.

Mean age at presentation for boys: 6.1 yrs

Mean age at presentation for girls: 5.5 yrs

Age- sex distribution:

AGE	MALE	FEMALE
< 1 YEAR	8(72.7%)	3(27.2%)
5 YEAR	58(61.7%)	36(38.2%)
>5YEAR	74(77%)	22(22.9%)

In the present study, of the 11 children below 1 year,72.7% were males and 27.2% females. Among the children between 1 – 5 years,61.7% males and 38.2% females .and > 5 years ,77% males and 22.9% females .in all age groups ,males were predominant .

Nutritional status: Of the 201 children analysed, 91(45.3%) were undernourished as per WHO standards(weight for age < 2 Standard deviation) and 110 (54.7%)were well nourished.

UNDERNOURISHED	WELL NOURISHED
91	110
45.3%	54.7%

Age versus nutritional status

As per WHO standards, 63.6% of children < 1 yr were well nourished and 36.3% were undernourished. In age group between 1 – 5 yrs, 58.5% were well nourished and 41.4% were undernourished. Above 5 yrs ,50% undernourished and 50% well nourished

NUTRITIONAL STATUS

	< 1 YEAR	1– 5 YEAR	>5 YEAR
WELL NOURISHED	7(63.6%)	55(58.5%)	48(50%)
UNDERNOURSISHED	4(36.3%)	39(41.4%)	48(50%)

P valve :0.414

Sex versus nutritional status: Of the total 61 females, majority (52.45%) were undernourished as against 47.54% well nourished .In male population, only 42.14% were undernourished and 57.85% were well nourished. There was no statistical significance between two groups with p valve 0.176

	MALES	FEMALES
Well nourished	81(57.85%)	29(47.54%)

Under nourished	59(42.14%)	32(52.45%)

Symptom –diagnosis interval ;

The mean symptom diagnosis interval (SDI) was 20.67±14.801days. The range was 5 to 90 days. The mean SDI in the WN group was 19.84±13.879 days and 21.67±15.865 days in the UN group.The difference between the two groups was not statistically significant .(p =0.383)

NOURISHMENT	MEAN SYMPTOM-DIAGNOSIS INTERVAL
WELL NOURISHED	19.84±13.879
UNDERNOURISHED	21.67±15.865

Total leucocyte count at admission: The mean TLC at admission was 38679.60±82105.955.There were 85 (42.2%) children with a TLC of <10,000;73(36.3%) with a TLC between 10,000 -50,000 ; 31(15.4%) children with a TLC of 50,000-100,000 and 12 (6%) children with TLC of > 100,000.

The ratio of WN and UN children in all 3groups was analysed. In children with TLC <10000, 56.5% were WN and 43.5% were UN. In children with TLC between10,000 and 50,000 ,50.7 %were WN and 49.3% were UN. In children with TLC 50,000-1,00,000 ,64.5% were WN and 35.5% were UN & in children with TC >100,000 50% were undernourished & 50% well nourished. **There was no statistical difference between the two groups (p =0.456)**

TLC	TOTAL	WELL NOURISHED	UNDERNOURISHED
<10000	85	48(56.5%)	37(43.5%)
10000-50007	3	37(50.7%)	36(49.3%)
0			
50000-100031		20(64.5%)	11(35.5%)
00			
>1,00,000	12	6(50%)	6(50%)

Haemoglobin at admission:

The mean haemoglobin level at admission was 6.924±4.34 g/dl.

The mean haemoglobin in well nourished children is 7.16±5.93 as against 6.72±2.31 g/dl..There was no statistical difference between the UN and WN children with p valve of 0.425

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NUTRITIONAL STATUS	Hemoglobin (g/dl) mean / standard deviation
WELL NOURISHED	7.162+5.9396
UNDERNOURISHED	6.727+2.3132

Of the 91 undernourished children ,37.36% had Hb level < 5 g/dl,34.06% had Hb level between 5 – 8 g/dl, 27.47% had Hb between 8 -11 g/dl and 0.01% had more than 11g/dl. Among the well nourished children, 22.72%had Hb level of less than 5 g/dl,40% had between 5 to 8 g/dl, 31.80% had 8-11 g/dl and 5 % of them with Hb valve of more than 11 g/dl

LEVELOFUNDERNOURSHED WELL NOURISHED

HEMOGLOBIN

<5	34(37.36%)	25(22.72%)
5-8	31(34.06%)	44(40%)
8-11	25(27.47%)	35(31.80%)
>11	1(0.01%)	6(5%)

No of children presented with severe anemia on admission:

	< 5 g/dl	>5 g/dl
WELL NOURISHED	25	85
UNDERNOURISHED	34	57

Platelet count at admission:

The mean platelet count was 43,833.33±65,167 /cu mm ,range between

1000-3,24000/cu mm. On analysing the severity of thrombocytopenia based on nutritional status.

Of the 91 undernourished children,46.15% had platelet count <20,000,46.15% had platelet count between 20,000-1 lakh &7.7% had platelet count >1 lakh. Among well nourished children, 55.5% had platelet count < 20,000 ,33.6% had platelet count between 20,000-1 lakh and 10.9% had platelet count >1 lakh

PLATELET COUNT	WELL NOURISHED	UNDERNOURISHED
<20,000	61(55.5%)	42(46.2%)
20,000-1,00,000	37(33.6%)	42(46.2%)
>1,00,000	12(10.9%)	7(7.7%)

X RAY FEATURES:

On evaluation of radiological features, 156 (77.6%)had normal x ray,24(12%) had leukemic knee deposites ,17(8.5%) had mediastinal widening ,2 (1.5 %) had osteolytic changes and only 1(0.5%)had cardiomegaly

X RAY FINDING	NO OF CHILDREN	PERCENTAGE
NORMAL	156	77.6%
LEUKEMIC KNEE DEPOSITES	24	12%
MEDIASTINAL WIDENING	17	8.5%
OSTEOLYTIC LESIONS	2	1.5%
CARDIOMEGALY	1	0.5%

USG findings:On evaluating USG features,majority had hepatosplenomegaly (38.8%),followed by only hepatomegaly in 24.9% children,22.8 % had hepatosplenomegaly with paraaortic nodes,8.9%had renomegaly,0.49%had bowel wall thickening &uterine enlargement only 7% had normal USG.

USG FINDING	NO OF CHILDREN	PERCENTAGE
HEPATOMEGALY	50	24.9%
	70	38.8%
HEPATOSPLENOMEGALY		
HEPATOSPLENOMEGALY	46	22.8%
PARAAORTICLYMPH NODES		
RENOMEGALY	18	8.9%
BOWELWALL THICKENING	1	0.49%
RENAL CALCULI	1	0.49%
NORMAL	14	7%

Morbidities during therapy:Requirement of PRBCs transfusions:

	PRBC transfusion
NOURISHMENT	(mean/standard deviation)
UNDERNORISHED	1.88±0.687
WELLNOURISHED	1.66±0.654

P valve significance (p =0 .020)Each Undernourished child had a requirement of 1.88+0.687 blood transfusions at the time of admission as against 1.660+0.654. in well nourished child. The statistical difference between the two groups is significant with a p value of 0.020.($p < 0.05$)

Requirement of platelet transfusion:

NOURISHMENT	PLATELET TRANSFUSION (mean/standard deviation)
UNDERNOURISHED	2.24 ±0.877
WELL NOURISHED	1.94±0.725

P value significance (p=0.012)

Each undernourished child had a requirement of 2.24+0.877 platelet transfusion as against 1.94+0.725 in well nourished child.The statistical difference between two groups is significant with a p value 0f 0.012

FEBRILE NEUTROPENIA:

77 children in the study population had an episode of febrile neutropenia which accounts to 38%. On evaluating based on their nutritional status , 49 children had developed febrile neutropenia in undernourished children as against 28 children had febrile neutropenia in wellnourished children with significant p value of 0.00007

	UNDER NOURISHED(91)	WELL NOURISHED(110)
FEBRILE NEUTROPENIA	49(53%)	28(28%)

INFECTIONS: Of the total 201 children ,129(64%) children developed significant infection during the course of the treatment . The following were the infection encountered during the course of the therapy

	UNDERNOURISHED	WELL NOURISHED	P value
INFECTIONS	62(68.1%)	67(60.9%)	0.479
PNEUMONIA	15(16.5%)	10(9.1%)	0.196
TUBERCULOSIS	1	-	0.270
HBsAg	11(12.1%)	10(9.09%)	0.10
MENINGITIS	5(5.5%)	7(6.4%)	0.450
SEPSIS	**14(15.3%)**	**5(4.5%)**	**0.0176**
UTI	6(6.3%)	7(6.5%)	0.542
HIV	2	1	0.453
Chicken pox	3	1	0.227

Herpes zoster	2	2	0.847
HEPATITIS	18(19.7%)	22(20%)	0.229

URINARY TRACT INFECTIONS:

	ECOLI	KLEBSIELLA	PSEUDOMONAS
WELL NOURISHED	4	3	-
UNDERNOURISHED	3	2	1
TOTAL	7	5	1

The commonest organisms encountered in urinary tract infection is e.coli (53.84%),followed klebsiella oraganism in 38.46% and pseudomonas in 7.6 % of children

SEPSIS;

	ECOLI	KLEBSIELLA	STAPYLOCOCCUS	PSEUDOMONAS	CANDIDA
UN-N	3	1	4	2	4
WELL N	-	1	1	-	2

The commonest infection encountered in sepsis was candida(33.3%),followed by stapylococcus(27.7%),ecoli (16.6%)&klebsiella(11.1%).

OUTCOME:

Of the 201 children studied in the present study, only 46 children (22.88%) are survivors,52 (25.87%)childre relapsed,52 (25.87%) of them died and 51(25.37%)were defaulters

OUTCOME	NO OF CHILDREN	PERCENTAGE
WELL	46	22.88%
RELAPSE	52	25.87%
DIED	52	25.87%
DEFAULTER	51	25.1%

OUTCOME PREDICTORS

Age:

AGE	WELL	RELAPSE	DIED	DEFAULTER

<1 YR	1(9.1%)	-	6(54.5%)	4(36.4%)
1-5 YR	26(27.7%)	20(21.3%)	25(26.6%)	23(24.5%)
>5YR	19(19.8%)	32(33.3%)	21(21.9%)	24(25%)

The percentage of children who survived among <1 year,1-5 yrs and > 5 years were 9.1%,27.7% and 19.8% respectively. The percentage of relapsed children between 3 groups were 0%,21.3% and 21.9%respectively and the percentage of death between the three groups were 54.5%,26.6% and 21.9% respectively .There was statistical significance between the groups with p valve of 0.049

OUTCOME OF CHILDREN LESS THAN 1 YEAR:

On analysing the outcome of children < 1 yr and >1 yr .the percentage of death was high in children less than 1 yr accounting to 54.5% and in children 1 yr ,percentage of death was 24.2%. the difference in the outcome was statistically significant with p valve of 0.014

	WELL	RELAPSE	DIED	DEFAULT
< 1 yr	1	-	6	4
>1 yr	45	52	46	47

SEX :

	WELL	RELAPSE	DIED	DEFAULT
MALES	34	39	30	37
FEMALES	12	13	22	14

Among the females, only 12(19.7%)children were survivors, 13 (21.3%)relapsed,22 (36.1%)expired and 14 (23%)were defaulters and among males ,34 (24.3%) were survivors,39(27.9%) relapsed ,30 (21.4%)died and 37 (26.4%)defaulters.there was no statistical significance between the 2 groups.

P VALUE ;0.185

TOTAL LEUCOCYTE COUNT ;

	WELL	RELAPSE	DIED	DEFAULTER
< 5000	9(25%)	8(22.2%)	13(36.1%)	6(16.7%)
5000-50,000	30(24.5%)	29(26.2%)	21(20.4%)	35(28.7%)

50,000-1,00,000	7(22.6%)	10(32.3%)	8(25.8%)	6(19.4%)
>1,00,000	-	5(16.7%)	10(50%)	4(33.3%)

The outcome of children with TLC <5000 ,5000-50,000,50,000-1 lakh and >1 lakh were compared. The difference was statistically significant with p valve of 0.034 .

2.Comparing the outcome of the children with TLC <100,000 to >100,000.

	WELL	RELAPSE	DIED	DEFAULT
<100,000	46	47	42	47
>1,00,000	-	5	10	4

The outcome of the children with TLC < 1,00,000 and >1,00,000 were compared .the difference was statistically significant with p value of 0.013.

NUTRITIONAL STATUS & OUTCOME

NUTRITIONAL STATUS	WELL	RELAPSE	DIED	DEFAULTER
WELLNOURISHED	29(26.4%)	29(26.4%)	27(24.5%)	25(22.5%)
UNDERNOURISHED	17(18.7%)	23(25.3%)	25(27.5%)	26(28.6%)

Among the well nourished children , 26.4% survived ,26.4%relapsed,24.5% died and 22.5%defaulted from therapy.among undernourished ,18.7% survived,25.3%relapsed,27.5%died and 28.6% defaulted from therapy.the difference was not statistically significant.

By logistic regression analysis, independent predictors of mortality has been measured,

variables	Co-efficient	Std error	P value	Odds ratio	95%CI-LL	95%CI –UL
AGE< 1 YR	1.7243	0.7171	**0.0016**	**5.6089**	1.3754	22.8722

SEX	-0.8325	0.3602	0.0608	0.4350	0.2147	0.8811
SDI	-0.4119	0.5355	0.4417	0.6624	0.02319	1.8920
Hb	-0.0095	0.0461	0.8365	0.9905	0.9049	1.0843
TLC	1.3645	0.5186	**0.0085**	**3.9138**	1.4164	10.8149
UN/WN	-0.0065	0.3432	0.8464	0.9357	0.4775	1.8336

The factors that had significant effect on the outcome were age < 1 yr and total leucocyte count >1 lakh. They had a p value of 0.001 and 0.0085 respectively

DISCUSSION:

Mean age at onset: In the present study, the mean age at presentation was 5.8 yrs (range of 4 months- 12 years) when compared with the studies below:

Studies	Mean age	Range
St JUDE children research hospital	4 yrs	73% in 2 -9 yrs
Prokop et al in Germany	6 yrs	1-16 years

Ankara,turkey	7.35+38	1-14 yrs
Karachi, Pakisthan	6.5 yrs	-
NetajisubbashChandra bose hospital ,Kolkata	11yrs	1-25 yrs
Vellore hospital	6 yrs	1-14 yrs
	MEAN AGE	**RANGE**
Present study	**5.8 yrs**	**4months-12years**

Sex disparity:

In the present study, the glaring male predominance (69.7%) was noted. This male preponderance was consistent with that seen in the rest of the world and our own country as shown below

STUDIES	MALE:FEMALE RATIO
St,Jude children research hospital	3.8:1

Prokop et al in Germany	2.2:1
Karachi,Pakisthan	1.7:1
Tatamemorial hospital/AIIMS,delhi	2.9:1
PRESENT STUDY	2.29:1

Nutritional status:

In the present study , 45% of the children were underweight according to the WHO standards(Z< 2 SD). This is less than the overall data from other parts of our country. The difference in nutritional status between the girls and the boys was not statistically significant(p=0.77).

STUDY	% of undernutrition at presentation(weight for age)
Maulana Azad medical college ,new delhi	56.8%

PGIMER,Chandigarh	52%
Kuala, lumpur	37.3%
Turkey	56.8%
Mexico	37%
Present study	45%

Symptom diagnosis interval:

The mean symptom diagnosis interval was 20.67±14.80 days. The mean SDI in WN children is 19.84±14.80 days and 21.67±15.865 days in UN children .The difference between the two groups was not statistically significant (p= 0.383)

This delay in diagnosis is related to the poor socioeconomic status and low educational status. Lack of parental education and little awareness of health issues delay the seeking of medical help. In addition, limited knowledge and subsequent late recognition by the health care providers in rural areas may delay the referral to higher centre. Consequently children have more advanced stage at diagnosis.

Haemoglobin level at presentation;

The mean Hemoglobin was 6.924 ±4.304 g/dl. The mean Hb in WN children

was 7.162±5.9396 and 6.727 +2.3132 in UN children.The difference between two groups was not statistically significant (p).but the no of children who had hemoglobin <5 g/dl was significantly high in37.36% UN children as compared to 22.72% WN children (p 0.0233)

Total leucocyte at admission:

study

1 lakh
St Jude hospital

14%

UK

12%

germany

11.3%

Dana farber consortium U.S

10.9 %

Cancer institute chennai

23.2%

Tata memorial hospital

14.6%

AIIMS

18%

PRESENT STUDY >1 LAKH:9.9% >50,000:21.3%

We have 9.9 % children with TLC > 1,00,000 and 21.3% children with TLC >50,000 at admission. As compared with other studies, our population had more no of children with TLC > 50,000. The difference noted is possibly due to heterogeneity in the population and the geography of the country

Morbidities :

Requirement of blood and platelet transfusion:

Each Undernourished child had a requirement of 1.88±0.687 blood transfusions at the time of admission as against 1.660±0.654 in well nourished child The statistical difference between the two groups was significant with a p valve of 0.020.($p < 0.05$)

Each undernourished child had a requirement of 2.24+0.877 platelet transfusion as against 1.94+0.725 in well nourished child. The statistical difference between two

groups was significant with a p valve 0f 0.012.

Febrile neutropenia:

In the present study, 53% of undernourished children had febrile neutropenia as against 25% in well nourished children with p valve significance (0.00007).This observation correlates with that of a study from Maulana Azad Medical College, Delhi was has also shown an higher incidence of febrile neutropenias (32%) in the UN group as compared to 28% in the WN group.[75] In a study in the USA the mortality rate in children with cancer because of febrile neutropenia given as 3%[88].

Infections encountered in the study:

The following studies has shown that the children with ALL had more no of infection as against normal population with significant p valve < 0.01

STUDY	RESULTS	PRESENT STUDY
FINLAND	Respiratory tract infection (44%)	Pneumonia (12.34%)
Ann academic medical college ,Singapore	Respiratory tract infection	
King abdul aziz hospital, Saudi Arabia	Hepatitis-80% 9.8% positive for HBsAg	Hepatitis(19.90%) HBs Ag 10.94%

Kidwai ,memorialSepsis (gram negativeSepsis (9.4%)
institute , Bangalore bacteria) Fungalsepsis (commonest sepsis)

In my present study, 64% of the children had significant documented infection.68% of undernourished children and 60% of well nourished children had significant infection. The difference between the two groups was not statistically significant. Of all the documented infection ,sepsis have occurred in more no of children among undernourished as compared

to well nourished children the p valve significant. The fungal sepsis were the commonest documented infection .

Outcome of the study population:

Analysing the outcome in 201 children, 46 (22.88%) were survivors, 51 (25.37%)dropped out,52 (25.87%) expired and 52 (25.87%) relapsed.

Prognostic factors:

Age :

Age has remained an independent predictor of outcome. In the present study, Children aged > 1 yr have a better disease free survival than infants (p 0.0414) . Infants and adolescents have a less favorable prognosis than children between 1 and 10 years of age. However, contemporary intensive treatment regimens have decreased the effect of age. In the Nordic series , infants fare worse than older children, but the difference between adolescents (>10 years of age) and other children older than 1 year is very slight. In the MRC UKALL X and Xa trials, age was an independent prognostic factor in a mixed

population of children (excluding infants under 1 year of age) and adults .[91,92,93,04]

In the BFM-90 study, children aged 1-9 years had a favourable outcome. The CCG also had a worse prognosis in children aged 10 or more years as compared with younger non infants . The same trend has been shown in

studies performed by many major co-operative study groups (POG, MRC, SJCRH, Italian Association of Pediatric Hematology and Oncology (AIEOP), Dutch Childhood Leukemia Study Group (DCLSG), COALL, Children Leukemia Cooperative Group (CLCG-EORTC) and TCCSG).[91,92,93,94]

Among the Indian studies, a study from Tata Memorial Hospital , Mumbai , age at presentation did not have a significant effect on the outcome as per the univariate and multivariate analyses.

At the study done in Cancer institute , Chennai the effect of age was not significant with univariate p value of 0.16. in the study done in AIIMS , New Delhi age was non significant with p values of 0.1 and 0.2 respectively.[8]

Infants with ALL have a very high risk of treatment failure. This is partly related to the higher incidence of unfavourable very immature pro B –cell ALL prototype and presence of mixed lineage gene rearrangements

sex: The difference in outcomes between males and females was not significant with a p value of 0.892

study	Outcome – girls	Outcome – boys
Pui & co workers (1960)	43.1%	31.5%
Pui & co workers (1991-94)	84%	71%
Nordic patients	59%	48%
BFM-90	82%	75%
Present study	27.86%	20.71%

In contrast to other studies, 27.86% of the boys were survivors as against 20.17% in girl. Indian studies from various centres does not show sex difference in the outcome. One reason for the better prognosis for girls shown in some studies because of the occurrence of testicular relapses among boys, but boys also appear to be at increased risk of bone marrow and CNS relapse for reasons that are not well understood. However, in clinical trials with high 5-year EFS rates (>80%), male gender is not an adverse risk factor.

Total leucocyte count : In our study we found that a high TLC at presentation

(>1,00,000/cu.mm) have a worse outcome. The difference was statistically significant between children with a TLC of <1,00,000/cu.mm and those with TLC of > 1,00,000/cu.mm(p =0.013).When children with TLC <50,000/cu.mm, 50,000/cu.mm – 1,00,000/cu.mm and >1,00,000/cu.mm were compared, the outcomes differed significantly(p =0.0384).

In a study done in Poland, from 1981 to 1986, in children with ALL an initial WBC above 50,000/mm3, achieved significantly worse treatment results than children with lower WBC. The 6-year disease-free survival being 33% and 60%. In the Nordic study, the 5- year event-free survival (EFS) for children with WBC 50-100x109/L is 67.3%. The EFS continues to decline with the elevation of the lower cut-off point being 41.3% WBC >100x109/L and 30.2% in WBC > 200x109/L .

In the multicentric Indian study , it was found that TLC at presentation was not significantly associated with toxic death in any of the 3 centres. Conversely TLC might be expected to have a greater prognostic significance in populations with lower toxic death rates. The univariate p values for the effect of TLC on Disease Free Survival were 0.0002 , 0.0011 and 0.066 respectively in Mumbai, New Delhi and Chennai respectively.[8]

Nutritional status:

In our study, undernutrition (indicator weight for age) did not influence in the outcome in the children with ALL.

In a study done in Spain in 43 patients ,undernourished children(n = 16) had a significantly worser outcome than well nourished children(n=27). The 5 year survival rate was 83% for well nourished children and only 26% for undernourished children($p < 0.001$). [9]

In another Mexican study it has been seen that five year disease free-survival was 65% and 7% for children receiving either optimal and sub-optimal doses of maintenance chemotherapy (p less than 0.001) respectively .Suboptimal doses of chemotherapy were delivered mainly in undernourished children. They summarized malnutrition to have an adverse impact on survival in ALL..Another Mexican study in 500 ALL patients has given DFS for WN children to be 75% as compared to 26% in UN children.[35]

In Pakistan a study done at Lahore on 100 patients with ALL did not show any difference in the survival ,[38] death and relapse when they compared the UN and WN children. A study in Scotland compared BMI to survival.They did not find any evidence of BMI being related to the clinical outcome.[40]

Though there are multiple studies that stress the importance and poor prognostic role of malnutrition at diagnosis in the outcome of patients with ALL.

In the Indian collaborative trial nutritional status was not seen to be a risk factor influencing outcome and survival.

SUMMARY:

201 children with ALL were studied (registered between Jan 2000 – Dec 2005)
The mean age of presentation was 5.8 yrs(4 months – 12 yrs) .There was no difference between the age of presentation between boys and girls.
The male to female ratio was 2.29:1.
5.4% children were below 1year of age.
45% children were undernourished at presentation as per the WHO standards.
The nutritional status was the same amongst boys and girls.
21.50% children had a presenting TLC of >50,000/cu.mm. and 9.9% had a TLC >1,00,000 at diagnosis.
The presenting TLC was similar in the UN and WN groups.
The no of children presented with severe anemia was high in UN as compared to WN (p value :0.0233)
The mean SDI was 20.67±14.801days.This was similar in the WN &UN group.
The morbidity –Requirement of platelet and blood transfusion at the time of admission were high in undernourished children as compared to well nourished children .(p 0.020 and 0.012 respectively)

53% of undernourished children had an episode febrile neutropenia as compared to 29% in well nourished children(p 0.0007)
Sepsis was documented in higher no of undernourished children as compared to well nourished children (p 0.0176)
Fungal sepsis were the commonest infection encountered in undernourished children
In this study,22.88% children are survivors. The difference in survival between the UN and WN group is not significant
Mortality accounts to 25.87% and relapse accounts to 25.8%
On analysing the prognostic factors , age less than 1 year and TLC > 1,00,000 was associated with poor prognosis both by univariate and multivariate analysis with p value of 0.014 and 0.0016 respectively
No difference was seen in the mortality rate in the WN and UN group .

CONCLUSION:

The overall survival in 201 children treated for ALL using the BFM protocol was 22.8%..

The most important prognostic indicator for outcome is TLC and age.

Children with a high TLC (>1,00,000/mm^3)have an mortality rate of 50%.

.Children less than 1 year also had a worst outcome .

Higher incidence of febrile neutropenia and sepsis was seen in undernourished children as compared to well nourished children.

.Nutritional status(indicator weight for age) did not influence the outcome of the children with ALL

PROFORMA (Annexure I)

Name : Father's Education

H No. Mother's Education

DOB Urban / Rural

Sex :

Date of Diagnosis

Date of last evaluation

Age of diagnosis (month)

Symptoms – Diagnosis interval

Type of ALL

Hb at admission

TLC

Platelet

Weight at admission

Height at admission

Serum albumin

x ray

USG abdomen

Nutritional status according to WHO standard charts

Well nourished / under nourished

Hepatitis /HBsAg positives

HIV status (inc both parents)

Date

Admission

Blood transfusion (at presentation)

Platelet transfusion (at presentation)

Febrile neutropenia

Site (focus)

Blood

C/S

Other C/S

Fever without neutropenia

Status last evaluation

1. Well
2. Relapsed
3. Died
4. Treatment defaulter

Duration off therapy

_____months

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